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Reproductive Axis after Discontinuation of Gonadotropin-Releasing Hormone Analog Treatment of Girls with Precocious Puberty: Long Term Follow-Up Comparing Girls with Hypothalamic Hamartoma to Those with Idiopathic Precocious Puberty

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ABSTRACT

Although the GnRH agonist analogs have become an established treatment for precocious puberty, there have been few long term studies of reproductive function and general health after discontinuation of therapy. To this end, we compared peak LH and FSH after 100 μg sc GnRH, estradiol, mean ovarian volume (MOV), age of onset and frequency of menses, body mass (BMI), and incidence of neurological and psychiatric problems in 2 groups of girls: those with precocious puberty due to hypothalamic hamartoma (HH; n = 18) and those with idiopathic precocious puberty (IPP; n = 32) who had been treated with deslorelin (4–8 μg/kg·day, sc) or histrelin (10 μg/kg·day, sc) for 3.1–10.3 yr and were observed at 1, 2, 3, and 4–5 yr after discontinuation of treatment. The endocrine findings were also compared to those in 14 normal perimenarcheal girls. There were no differences between the HH and IPP groups in age or bone age at the start of treatment, at the end of treatment, or during GnRH analog therapy. We found that whereas the peak LH level was higher in HH than in IPP girls before (165.5 ± 129 *vs.* 97.5 ± 55.7; $P < 0.02$) and at the end (6.8 ± 6.0 *vs.* 3.9 ± 1.8 mIU/mL; $P < 0.05$) of therapy, this difference did not persist at any of the posttherapy time points. LH, FSH, and estradiol rose into the pubertal range by 1 yr posttherapy in both HH and IPP. However, the mean posttherapy peak LH levels in both HH and IPP groups tended to be lower than normal, whereas the peak FSH levels were not different from normal, so that the overall posttherapy LH/FSH ratio was decreased compared to that in the normal girls (HH, 2.7 ± 0.3; IPP, 2.6 ± 0.1; normal, 5.2 ± 4.8; $P < 0.05$). The MOV was larger in HH than IPP at the end of treatment (3.7 ± 3.5 *vs.* 2.0 ± 1.2 mL; $P < 0.05$) and tended to increase in both groups over time to become larger than that in normal girls by 4–5 yr posttherapy (HH, 14.9 ± 12.9; IPP, 7.6 ± 2.2; normal, 5.4 ± 2.5 mL; $P < 0.05$). Whereas the onset of spontaneous menses varied widely in both groups, once menses had started, the HH group had a higher incidence of oligomenorrhea. Pelvic ultrasonography revealed more than 10-mm hypoechoic regions in 4 HH patients, 15 IPP patients, and 3 normal girls, all of whom were reporting regular menses. Live births of normal infants were reported by 2 HH and 2 IPP patients, and elective terminations of pregnancy were reported by 1 HH and 2 IPP patients. BMI was greater than normal in HH and IPP both before treatment and at all posttherapy time points and tended to be higher in the HH patients. Marked obesity (BMI, +2 to +5.2 SD score) was observed in 5 HH and 6 IPP patients, 1 of whom had a BMI of +2.5 SD score and developed acanthosis nigricans, insulin resistance, and hyperglycemia. Seizure disorders developed during GnRH analog therapy in 5 HH and 1 IPP patient, and 2 additional HH girls developed severe depression and emotional lability posttherapy. Although the mean anterior-posterior dimension of the hamartoma was larger in the HH patients with seizure than in those who were seizure free (1.7 ± 1.2 *vs.* 0.9 ± 0.4 cm; $P < 0.05$), no change in hamartoma size was observed either during or after therapy, and no patient has reported the onset of a seizure disorder posttherapy. Other than a tendency toward a larger MOV, a higher incidence of oligomenorrhea, obesity, and frequency of neurological disorders, recovery of the reproductive axis after GnRH analog therapy was not markedly different in HH compared to IPP. Continued follow-up of these patients may determine whether the decreased LH responses and increased BMI in both groups compared to those in normal girls remain clinically significant problems. (*J Clin Endocrinol Metab* **84:** 44–49, 1999)

THE ASSOCIATION of hypothalamic hamartoma (HH) with precocious puberty is well established (1, 2). Whereas children with HH often present at an earlier age and with higher gonadotropin responses after administration of exogenous GnRH than do children with idiopathic precocious puberty (IPP), their clinical response to treatment with the long acting GnRH agonist analogs has not differed from that of patients with IPP (3–5). In addition, most, but not all (6), imaging studies have indicated that hamartoma size remains stable during and after treatment (7), and short term follow-up studies have to date not reported a higher frequency of delayed menses, infertility, or other neuroendocrine complaints in girls with HH (5, 8, 9).

To assess the long term recovery of the pituitary-gonadal axis after discontinuation of GnRH analog therapy and to determine whether patients with hamartoma might be at increased risk for posttherapy reproductive disorders, we compared our findings in girls with precocious puberty and HH to those in girls with a diagnosis of IPP. To control for biases that could overestimate the incidence of adverse effects because one group was treated longer or began treatment at an earlier age, we selected a subgroup of IPP patients

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for whom age at the start of therapy (and hence the duration of therapy) was not different from that for the group of patients with HH. Patients were treated with GnRH analog for 3.1–10.3 yr (mean, 6.8 ± 1.9 yr) and were followed for 3–8 yr after treatment was stopped.

Subjects and Methods

Eighteen girls had precocious puberty due to HH, and 32 had IPP. All began GnRH analog treatment at less than 7 yr of age and had been observed for at least 3 yr after discontinuation of therapy. There were no significant differences between the girls with HH and those with IPP in mean ± SD chronological age (CA; 4.3 ± 1.6 *vs.* 4.5 ± 1.7 yr) or bone age (BA; 8.5 ± 2.3 *vs.* 8.8 ± 3.1 yr) at the start of therapy, in the length of GnRH analog treatment (7.2 ± 2.1 *vs.* 6.6 ± 1.8 yr), or in CA (11.3 ± 0.8 *vs.* 11.1 ± 0.8 yr) and BA (12.8 ± 1.2 *vs.* 12.4 ± 1.2 yr) at discontinuation of treatment.

The diagnosis of hamartoma was based on the finding of an isodense, pedunculated, nonenhancing mass in the area of the mammillary bodies using computed tomography and/or magnetic resonance imaging. Patients with nonhamartomatous intracranial masses (*i.e.* glioma or astrocytoma) or with gonadotropin-dependent puberty secondary to a gonadotropin-independent process (*i.e.* congenital adrenal hyperplasia, familial male precocious puberty, or McCune-Albright syndrome) were not included in this analysis.

Patients were treated with either deslorelin (D-Trp^6,Pro^9,NEt-LHRH; 4–8 μg/kg·day, sc; 46 patients) or histrelin (D-His[Bzl]^6,Pro^9,Net-LHRH; 10 μg/kg·day; 4 patients). Therapy was discontinued in most cases at the age when normal puberty would be expected (10–12 yr), but earlier (8–9 yr) in 2 patients (1 HH and 1 IPP) at the request of the family and patient. After discontinuation of treatment, girls were evaluated at 1- to 2-yr intervals at the Clinical Center at the NIH. Immunoreactive LH and FSH were measured (10) from 0–120 min after the iv administration of 100 μg GnRH at 0900 h. Serum estradiol (E_2) was measured (11) at 0 min. Ovarian structure and dimensions were assessed using pelvic ultrasonography, and mean ovarian volume (MOV) was estimated using the formula: MOV = volume of left ovary + volume of right ovary/2. The frequency of menses was determined from monthly diaries maintained by the patient and her family. Because menses were frequently irregular, the in-hospital endocrine evaluations were performed without regard to the phase of the menstrual cycle.

The body mass index (BMI) was calculated from weight (kilograms)/height (meters)^2, and the SD score was calculated from that of normal children using published standards (12).

For comparative purposes, we also measured LH and FSH (after administration of 100 μg GnRH), E_2, MOV, and BMI in 14 normal, postmenarcheal girls, aged 13.0–15.5 yr (mean, 14.0 ± 0.9), with breast pubertal stages IV–V.

Statistical analyses

Hormonal and MOV findings are presented as the mean ± SD of all patients in each group evaluated at baseline (yr 0, before discontinuation of GnRH treatment) and at the 1, 2, 3, and 4–5 yr points thereafter. Data from 4 and 5 yr visits were evaluated as the mean of yr 4 and 5, when both time points were available. Endocrine data from two HH patients were not available after 2 yr; hence, they have been excluded from the hormonal analysis.

Comparisons of hormonal parameters (gonadotropin and estrogen levels and ovarian volumes) and BMI were made using the *t* test. The frequency of menstrual bleeding was classified for each year as follows: 1, oligomenorrhea (menses at 60- to >150-day intervals); 2, irregular (every 35–60 days); and 3, regular (every 25–35 days). Comparisons between groups were made using the χ^2 statistic. When a diary was unavailable for a posttherapy year, the patient was excluded from that year's analysis of menses.

Results

LH and FSH after GnRH

Before the start of GnRH analog therapy, the HH group had significantly higher levels of peak GnRH-stimulated LH (165.5 ± 129 *vs.* 97.5 ± 55.7 mIU/mL; $P < 0.02$) and a higher peak LH/FSH ratio (5.4 ± 2.8 *vs.* 3.6 ± 2.4; $P < 0.05$) than the IPP group. At discontinuation of treatment (0 yr), the mean peak LH and FSH levels were also greater in HH than in IPP, but the groups did not differ in this respect at any of the subsequent posttherapy time points (Fig. 1, A and B). By 1 yr posttherapy, peak LH and FSH levels in both HH and IPP girls had entered the range for normal pubertal stage IV–V girls (13). However, the mean peak LH in both HH and IPP tended to be lower than that in normal girls at all time points, whereas the peak FSH levels were comparable to normal, so that the mean peak LH/FSH ratio for posttherapy yr 1–5 in both HH and IPP was lower than that in normal girls (HH, 2.7 ± 0.3; IPP, 2.6 ± 0.1; normal, 5.2 ± 4.8; $P < 0.05$).

Serum E_2, pubertal stage, and ovarian volume and structure

By 1 yr after stopping therapy and at all the subsequent time points, E_2 levels had risen from near or below the assay detection limit in both HH and IPP and were not different from normal (Fig. 1C). Breast development was pubertal stage III in 78% of HH and 79% of IPP girls at 0 yr, and had progressed to stage V in 53% of HH and 71% of IPP by 2 yr, in 81% of HH and 90% of IPP by 3 yr, and in all patients by 4–5 yr posttherapy.

The MOV was larger in HH than in IPP at discontinuation of therapy and at 4–5 yr, but was not significantly different at the intermediate time points. However, MOV tended to increase progressively in both groups over the first 3 yr after treatment was stopped and was significantly greater than that in the normal girls in HH at 3 yr and those in both HH and IPP at 4–5 yr posttherapy (Fig. 1D). Small (<1.0-cm) hypoechoic regions resembling follicles were observed in at least 1 posttherapy ultrasound study in 10 HH and 16 IPP girls and in 2 or more studies in 7 HH and 13 IPP girls. Larger, well circumscribed, more than 1.0-cm hypoechoic areas resembling cysts were observed at least once in 4 HH and 16 IPP girls and recurred once in 2 HH and 4 IPP girls. One IPP girl had recurrent, isolated, unilateral, 1.0- to 4.8-cm hypoechoic, cyst-like areas in both right and left ovaries at each yearly ultrasound study. Although the ultrasound appearance in this patient was suggestive of polycystic ovarian syndrome (14), she reported regular menses, she was not androgenized, and her LH levels were normal at baseline (4.2–6.8 mIU/mL) and after GnRH treatment (30.9–96.5 mIU/mL).

Two normal girls had multiple, bilateral hypoechoic areas, 0.2–1.0 cm in diameter. One asymptomatic normal girl had a large, unilateral hypoechoic area 5.0 × 8.0 cm in diameter, on a single ultrasound study.

Menses

The time interval between the discontinuation of GnRH analog and the start of spontaneous menses varied widely in both groups and was not significantly different in patients with HH (20.5 ± 16.3; range, 0–60 months) and those with IPP (17.6 ± 11.0; range, 5–61 months). One HH patient began menstruating before discontinuation of therapy despite a

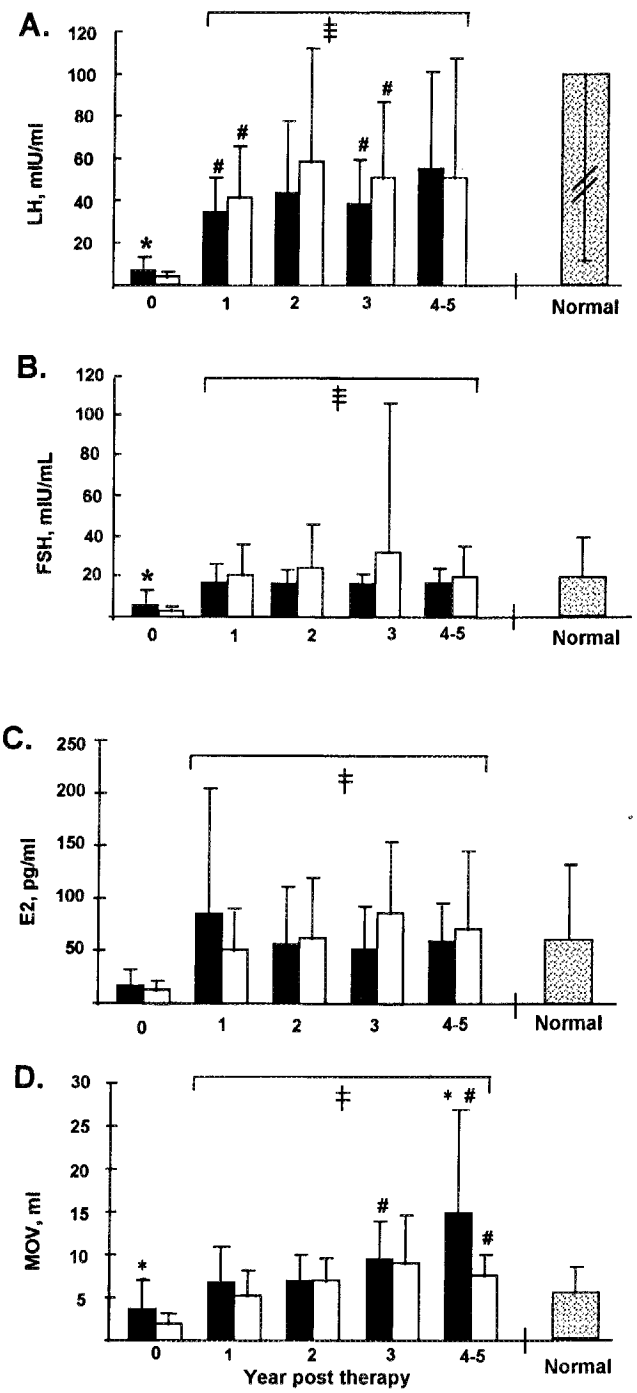

FIG. 1. Mean ± SD GnRH-stimulated LH (A) and FSH (B), E_2 (C), and MOV (D) at the end of GnRH analog therapy (yr 0) and at 1, 2, 3, and 4–5 yr post-therapy in girls with HH (*solid bars*), girls with IPP (*open bars*), and normal perimenarcheal girls (*textured bars*). *, $P < 0.05$ compared to IPP; #, $P < 0.05$ compared to normal girls; ‡, $P < 0.05$ compared to yr 0; ‡, $P < 0.001$ compared to yr 0.

2-fold increase in the dose of GnRH agonist and apparently good compliance, and 1 other HH patient had persistent primary amenorrhea, although she had withdrawal bleeding after a 10-day challenge with medroxyprogesterone acetate at 4 yr posttherapy. There were no significant differences between the groups in the mean CA (13.4 ± 1.9 *vs.* 12.5 ± 0.7 yr) or BA (14.6 ± 1.3 *vs.* 13.8 ± 1.0 yr) at the onset of spontaneous menses. The number of girls reporting regular menses tended to increase in both groups over the 4 yr of follow-up; however, in the subset of girls who had begun spontaneous menses, a greater percentage of HH than IPP girls reported oligomenorrhea during yr 2 [4 of 13 (30%) *vs.* 0 of 24 (0%); $P < 0.005$] and yr 3 [3 of 13 (23%) *vs.* 1 of 31 (3%); $P < 0.05$] posttherapy (Fig. 2). The MOV was not significantly different in patients reporting oligomenorrhea *vs.* those with regular menses (7. 8 ± 2.9 *vs.* 5.6 ± 2.5 mL).

Seven girls (three HH and four IPP) have reported pregnancies; five pregnancies resulted in normal, live infants (one IPP girl was pregnant twice), two pregnancies were terminated electively, and one ended in spontaneous abortion in a girl with insulin-dependent diabetes mellitus (Table 1).

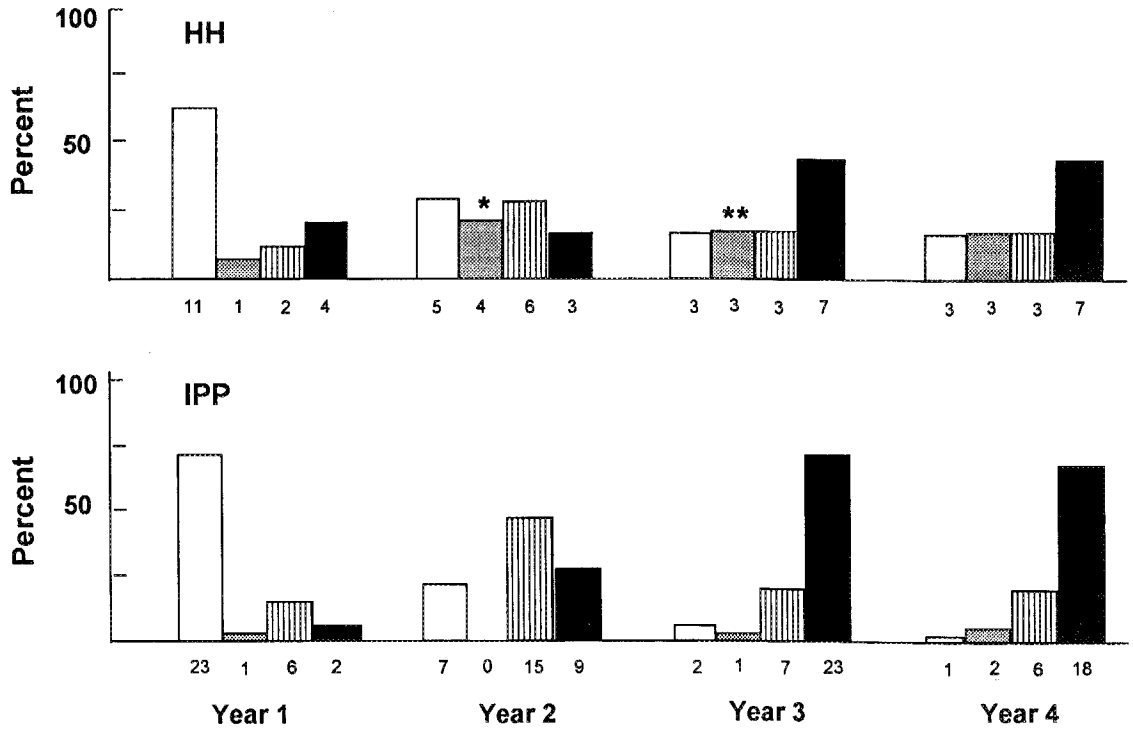

FIG. 2. Patterns of menstrual bleeding at 1, 2, 3, and 4 yr posttherapy in girls with HH (*upper panel*) and IPP (*lower panel*). *Column height* denotes the percentage of girls reporting no menses (□), oligomenorrhea (▩), irregular menses (▥), and regular menses (■). Figures *below each column* denote the number of patients. *, $P < 0.005$, HH *vs.* IPP; **, $P < 0.05$, HH *vs.* IPP.

TABLE 1. Diagnosis, duration of deslorelin therapy, time (months) posttherapy, age (years) at onset of menses, menstrual pattern, time (years) posttherapy, age (years) at end of gestation, and outcome in girls reporting pregnancy after discontinuing deslorelin treatment for precocious puberty

Patient no.	Diagnosis	Duration of therapy (yr)	Onset of menses: time, (months), post-treatment (age, years)	Menstrual pattern[a]	Conception: time, yr post-tx (age, years)	Outcome
1	HH	8.9	13 (12.4)	3	8.0 (19.4)	Normal female infant
2	HH	7.5	24 (12.4)	3	7.3 (17.7)	Abortion (elective)
3	HH	5.5	30 (13.0)	2	9.1 (19.5)	Normal male infant
4	IPP	6.0	16 (12.5)	2	4.7 (15.9)	Abortion (elective)
5	IPP	5.8	6 (12.6)	2	9.0 (20.9)	Normal female infant
6	IPP	5.1	13 (11.9)	3	6.0 (16.9)	Abortion (spontaneous)[b]
7	IPP	4.0	24 (12.5)	3	5.8 (16.3)	Normal male infant
					6.8 (17.3)	Normal male infant

[a] 3, Regular menses; 2, irregular menses.
[b] Patient was diabetic and receiving insulin therapy.

BMI (Fig. 3)

As expected, at the start of GnRH analog therapy, the mean BMI SD score of both HH (1.6 ± 1.2) and IPP (1.2 ± 1.3) girls was greater than that of normal girls of comparable age. At the end of therapy and at all the posttherapy time points, the mean BMI of both HH and IPP groups continued to exceed that of the normal girls, and marked obesity (BMI, 28.9–42.0, +2.0 to +5.2 SD score) was observed in five HH and in six IPP girls. Elective cosmetic breast reduction was performed in one HH and one IPP patient. The BMI and the incidence of obesity tended to be greater in HH than that in IPP, although this increase was not significantly different due to the wide variability among patients. Acanthosis nigricans (without clinically apparent insulin resistance) was observed in three HH girls with BMI values of +5.0, +3.0, and +0.9. Insulin resistance and hyperglycemia requiring treatment with oral agents and, eventually, insulin, was observed during and after GnRH analog therapy in one IPP patient who continued to menstruate regularly, but had mild hirsutism (BMI, +2.3) and reported a spontaneous abortion (see above).

Neurological abnormalities

Episodes of seizure, which were first noticed during the course of GnRH agonist therapy, were reported by 5 of 18 HH patients. Four patients were between 9 and 10 yr of age, and 1 was 11 yr. Anticonvulsants were used in all patients and were continued during and after discontinuation of GnRH analog therapy; however, 2 of these patients have been seizure free after discontinuation of anticonvulsant treatment. Diagnoses were reported as gelastic epilepsy in 1 girl and as

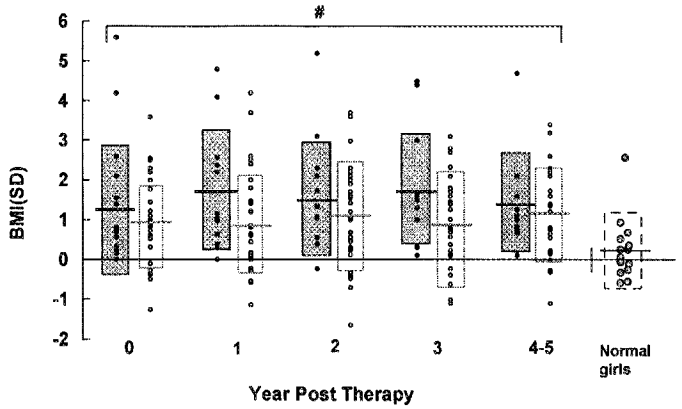

FIG. 3. Mean ± SD BMI SD score of girls with HH (*shaded bars*) and IPP (*open bars*) at the end of GnRH analog therapy and at 1, 2, 3, and 4–5 yr posttherapy. #, $P < 0.04$ compared to normal girls (*broken bar*).

complex partial seizure in 4 girls. No family has yet reported the onset of a seizure disorder after discontinuation of GnRH analog therapy. Emotional lability, depressive behavior, and mood swings without a diagnosis of seizure were reported in 2 additional HH patients after GnRH treatment was stopped. Whereas the mean hamartoma size was larger in HH girls reporting seizures than in those who were seizure free (maximum anterior-posterior diameter, 1.7 ± 1.2 *vs.* 0.9 ± 0.4 cm; $P < 0.05$) no girl had a documented change in the size of her hamartoma either during or after GnRH analog therapy.

A disorder diagnosed as benign nocturnal seizure of childhood developed during GnRH analog treatment in one IPP patient at 8 yr of age and was treated with anticonvulsants for 3 yr. This girl has been seizure free after discontinuation of GnRH analog.

Discussion

The GnRH agonist analogs have been used to treat many diverse reproductive system disorders, including precocious puberty. Initial clinical trials of these compounds appear to confirm their effectiveness and safety in suppressing gonadal activation and to document the reversibility of their effects in both adults and children. However, concerns have recently been expressed and are now widely disseminated via electronic media (15) that the GnRH analogs may have long lasting adverse effects on reproductive function as well as on physical and mental well-being. At present, there are few long term studies that address these issues objectively, particularly with regard to children with precocious puberty, many of whom are treated for long periods of time and from a very early age. To this end, we undertook to compare two groups of treated patients: girls with hypothalamic hamartoma and girls with idiopathic precocious puberty. We found that the reproductive axis appeared to have returned to normal in both patient groups by 4–5 yr after discontinuation of GnRH analog, but that the HH patients tended to have a higher incidence of irregular menses, obesity, and neurological and behavioral problems.

The pattern of relatively increased peak baseline LH and increased peak GnRH-stimulated LH/FSH ratio that we observed in the HH patients at initial presentation did not reemerge over the 5-yr posttreatment period. We did observe a significantly higher peak LH and increased MOV in the HH group at the end of treatment, and one such patient, with a MOV of 15.9 mL, who denied noncompliance, reported menarche and had a pubertal peak LH (28.8 mIU/mL) at 0 yr. Although these findings suggest resistance to GnRH analog or a higher pituitary gonadotropin reserve in HH, compliance may have been playing a major role despite the assertions of the patient and her family.

Although our findings confirm previous reports (5) that gonadotropin responses return to the normal range by 12 months after discontinuation of GnRH analog treatment, they also reveal that the peak GnRH-stimulated LH/FSH ratio after treatment tends to be low compared to that of normal girls. This may represent a blunted sensitivity to GnRH stimulation similar to that observed in normal women during the very early follicular phase of the menstrual cycle (16). However, it is not clear whether this is a consequence of prolonged suppression of the pituitary gonadotropes or represents the natural history of early maturation of the hypothalamic-pituitary-gonadal unit.

A previous study (7) indicated that ovarian volumes in girls who have stopped GnRH analog therapy return to pretreatment levels by 3 months and remain constant thereafter. However, these initial reports reflect findings in girls who were older (7.8 ± 1.1 yr) at the start of treatment and were treated for a shorter period of time (3.5 ± 0.9 yr) than those in the present groups. Our findings that ovarian volumes tend to increase progressively over the first 3 posttreatment years and were often larger than normal by 3 yr posttherapy suggest that recovery of the suppressed gonad of girls treated for longer periods of time may be a more gradual process, and that a complete picture of the effects of therapy may only emerge after several years have passed. The somewhat greater age and bone age at menarche, and the greater interval between discontinuation of therapy and menarche that we found in our patients compared to those reported by other observers (8) may also reflect the longer period of gonadal suppression and/or the early age when treatment was instituted. Nevertheless, it is reassuring that the mean age of menarche in our patients was comparable to that in normal girls and that seven patients have demonstrated fertility.

As has been noted by others (17), our patients' ovaries were larger than those of normal postpubertal girls (18) and were comparable in size to those of cycling mature women (19, 20). Hypoechoic, cyst- or follicle-like areas were detected in most patients at one or more posttherapy time points and in three normal girls. Whereas irregular menses and obesity were common complaints in our patients, none of the girls with persistent hypoechoic regions in their ovaries had the elevated baseline or GnRH-stimulated gonadotropin levels that would suggest true polycystic ovarian syndrome. Although acanthosis nigricans was observed in three HH patients, two of whom had oligomenorrhea and moderate to marked obesity, none of the three had clinical diabetes mellitus. Conversely, the IPP girl with insulin-dependent diabetes and mild hirsutism was having regular menses. Although we did not measure androgen levels in our patients, elevated adrenal androgen responses have been observed by

other groups (21) after GnRH analog treatment of IPP, and continuing follow-up will be needed to determine whether a fully developed polycystic ovary syndrome may eventually develop in any of these girls.

The timing of sexual maturation in normal females is linked to body fat content. Obese girls have earlier menarche than thin girls. Not surprisingly, as we and others (22) have reported, precocious puberty is also associated with increased body mass both at initial presentation and during GnRH analog treatment. Our current data show that this condition persists after discontinuation of therapy and progresses to frank obesity (BMI, >+2SD score) in many girls, more frequently in those with HH. Although it is tempting to implicate the hypothalamic abnormality in this trend toward obesity, there have been, to the best of our knowledge, only anecdotal reports (23) of an association between HH and extreme weight gain. Those who care for girls with precocious puberty may need to address this issue early in view of the morbidity that accompanies persistent obesity (24, 25).

HH has a known association with gelastic epilepsy (26, 27); however, only one HH patient carried this diagnosis, whereas four had partial complex seizure. In the HH patients as a group, seizures were associated with larger hamartomas, all seizures were first observed during GnRH analog treatment, and three of the six girls have been able to discontinue anticonvulsant therapy after stopping GnRH analog. Although it is not possible to determine from our data whether GnRH analog treatment delayed or, possibly, accelerated the onset of seizure in these patients, the lower incidence of seizure disorder in the IPP patients [1 of 32 girls; 3%, *vs.* 0.5% in normal children (28)] suggests that the preexisting neurological abnormality, rather than GnRH analog therapy, played the major roll.

Clinical trials using GnRH analogs to treat precocious puberty have not included untreated placebo control groups. Although the choice of an uncontrolled study design is understandable, it will be difficult to learn whether altered gonadotropin and gonadal androgen levels, changes in ovarian volume and structure, increased body weight, and neurological complications are a result of therapy or inevitable manifestations of the primary process. It is hoped that some or all of these issues will be resolved as these patients are followed throughout adulthood.

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